011253241
WPI Acc No: 1997-231144/*199721*
XRAM Acc No: C97-074352
Tablets with rapid disintegration in oral cavity - prepared by compressing and moulding mixture of medicine, crystalline cellulose, hydroxypropyl-cellulose and lubricant
Patent Assignee: RYUKAKUSAN KK (RYUK-N)
Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
JP 9071523	A	19970318	JP 95264583	A	19950907	199721	B

Priority Applications (No Type Date): JP 95264583 A 19950907
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
JP 9071523	A		5	A61K-009/20	

Abstract (Basic): JP 9071523 A
Tablets with rapid disintegration in the oral cavity are prepd. by compression and moulding a mixt. of a medicine, crystalline cellulose, lowly substd. hydroxypropylcellulose and a lubricant. Crystalline cellulose and lowly substd. hydroxypropylcellulose are used at ratios of 1:2 3-9.
Medicines which require rapid absorption (e.g. antihypertensive agents, cerebral circulation improving agents and anti-motion sickness agents are preferable used to prepare tablets.
USE - Used for chewable tablets.
ADVANTAGE - Rapid absorption of effective ingredients is obtained.
EXAMPLE - In an example, a compsn. of 10.0% meclozine HCL, 62.3% crystalline cellulose, 26.7% lowly substd. hydroxypropylcellulose and 1.0% Mg stearate was mixed and tabletted to give tablets. Tablets prepd. by compression pressure of 100, 200, 250 and 300 kgf showed disintegration period of 36.5, 27.3, 32.5, 40.1 and 54.0 sec., respectively.
Dwg.0/0
Title Terms: TABLET; RAPID; DISINTEGRATE; ORAL; CAVITY; PREPARATION; COMPRESS; MOULD; MIXTURE; MEDICINE; CRYSTAL; CELLULOSE; HYDROXYPROPYL; CELLULOSE; LUBRICATE
Derwent Class: A96; B07
International Patent Class (Main): A61K-009/20
International Patent Class (Additional): A61K-047/38
File Segment: CPI
? S PN=JP 08310969
S5 1 PN=JP 08310969
? T/5

5/5/1
DIALOG(R)File 352:Derwent WPI

(54)[Title of the invention] Tablet which is rapidly disintegrated in oral cavity

[Claims]

[Claim 1] A tablet which is rapidly disintegrated in oral cavity, which comprises a mixture of crystalline cellulose, slightly substituted hydroxypropylcellulose and lubricant, where in slightly substituted hydroxypropylcellulose and crystalline cellulose were mixed at 1:2.3 to 1:9 and compression-molded.

[Detailed description of the invention]

[0001]

[Technical field to which the invention belong] The present invention relates to the technical field of providing a composition of a rapidly disintegrating tablet which is immediately disintegrated by saliva in oral cavity or small amount of water without chewing and can be swallowed as it is or with water in oral cavity (hereinafter, referred to as rapidly disintegrating tablet) and a process for preparing the composition.

[0002]

[Prior art] As a preparation which can be taken without water, a chewable tablet is sold as a digestive medicine. This does not need drink such as water when it is taken, and this can be taken by immediately crunching in oral cavity when necessary. There can be found no preparation as a tablet which is rapidly

disintegrated without chewing in oral cavity and which allows a tablet to be easily swallowed.

[Problems to be solved by the invention]

[0003] Necessity of crunching at administration of the aforementioned chewable tablet is inconvenient to people having the small chewing ability such as senior. To patients having the small swallowing ability, a tablet which can be rapidly disintegrated in oral cavity and taken is useful.

[0004] The present invention was done from such the viewpoint and an object thereof is to provide a tablet which is rapidly disintegrated in a few tens seconds with saliva or small amount of water in oral cavity and is easily swallowed.

[0005] As a circumstance where the rapidly disintegrating tablet of the present invention is necessary, there are drugs which are required to be administered as a tablet without water, for example, motion sickness prevention drugs. In addition, the previous tablet requires that a patient having the little swallowing ability crushes the tablet and take it. The rapidly disintegrating tablet of the present invention is rapidly disintegrated in oral cavity, and is useful for a patient having the little swallowing ability to take the tablet. In particular, a rapidly disintegrating tablet is useful to a patient who can hardly swallow due to cerebral vascular disorder or bed ridden elderly patient. Examples of such the drug include a drug for hypertension and cerebral circulation and metabolism improving

drug.

[Means to solve the problems]

[0006] In order to solve the aforementioned problems, the present inventors adopted the following composition of an excipient and a disintegrating agent in a tablet.

[0007] That is, rapidly disintegrating tablet of the present invention is characterized in that slightly substituted hydroxypropylcellulose as a disintegrating agent and crystalline cellulose as an excipient are mixed at a ratio of 1:2.3 to 1:9, a lubricant is mixed therein and, if necessary, a coloring agent or the like is mixed therein, which is compression-molded into a tablet by compression.

[0008] As a drug to be contained in the rapidly disintegrating tablet of the present invention, meclizine hydrochloride which is a drug effective for treating motion sickness which has the antiemetic activity is useful. Examples of other drugs effective for treating motion sickness which has the antiemetic activity include, in addition to the aforementioned meclizine hydrochloride, dimenhydrinate, thielperazine, diphenhydramine salicylate+ diprophylline, promethadinetheocrate. Examples of the drug for hypertension include captopril, cilazapril, enarapril maleate and riconopril. Examples of the cerebral circulation and metabolism improving drug include drug cinarezine, vinpocetine, brovinecamine fumarate, pentoxifylline, cinepazied maleate,

trapidil, nicardipine hydrochloride, flunarizine hydrochloride, mecrophenoxate and ifenprodil tartrate.

[0009] The present invention will be explained below.

[0010] <1> Process for preparing the rapidly disintegrating tablet of the present invention

1) Composition

The present invention is characterized in that a rapidly disintegrating tablet is made by using following excipients and disintegrating agents which are generally used:

(1) Crystalline cellulose (excipient) (manufacture by Asahi Kasei Kogyo, Avicel PH-102, particle diameter 100 μm)

(2) Slightly substituted hydroxypropylcellulose (disintegrating agent)

(manufactured by Shientsu Kagaku Kogyo, L-HPC, particle diameter 160 μm, Japanese Pharmacopoeia 12th edition)

[0011] 2)Ratio of incorporation in the rapidly disintegrating tablet of the present invention

(1) Rapidly disintegrating tablet containing no drug

A mixture of 1% of magnesium stearate (lubricant:manufactured by Wakojunyaku Kogyo MS, particle diameter 70 μm), and each 99% or more of a mixture obtained by mixing slightly substituted hydroxypropylcellulose and crystalline cellulose at a ratio of 1:2.3 to 1:9, is used as an agent for compression.

[0012] (2) Rapidly disintegrating tablet containing a drug (meclizine hydrochloride)

A mixture of 10% of meclizine hydrochloride (antiemetic agent: manufacture by Nihonbulkyakuhin, molecular weight 481.89, melting point 270°C (dec.)), 1% of magnesium stearate, and 89% or more of a mixture obtained by mixing slightly substituted hydroxypropylcellulose and crystalline cellulose at a ratio of 1:4, is used as an agent for compression.

[0013] 3) Compression conditions for rapidly disintegrating tablet of the present invention

A tablet was prepared under the following conditions. Generally, it is said that a more molding load is applied, a hardness of a tablet grows larger, leading to difficult disintegration. However, in the rapidly disintegrating tablet of the present invention, there can be obtained a rapidly disintegrating tablet having a hardness at a molding load of 100 to 300 kgf (hereinafter, referred to as compression pressure).

Apparatus: N-20E-type double-press powder compressing machine (manufactured by Okadaseikou) pestle diameter 8.0 mm, radius of curvature 10R

Tablet weight: 200 mg

Compression pressure: 100 to 300 kgf

[0014] <2> Conditions under which effects of the rapidly disintegrating tablet of the present invention are measured

1) Measurement of tablet hardness

When a tablet has not a hardness to a some degree (hereinafter,

referred to as hardness), the tablet retains no original shape. The tablet is required that it has a hardness at a suitable compression pressure but is rapidly disintegrated. For this, a hardness was measured. In measurement of a sold plain tablet described below, that tablet had a hardness of 13 to 15 Kg. The rapidly disintegrating tablet of the present invention had the same level of a hardness.

Semiautomated hardness tester (TS-50 N-type, manufactured by Okadaseikou)

The stress required for compression breakage is measured and this is adopted as hardness (kg).

[0015] 2) Disintegrating property of a tablet

The disintegrating property of the rapidly disintegrating tablet was measured by a substitute test described below. The results of this test is correlated with the actual results in oral cavity. All of the rapidly disintegrating tablets of the present invention were disintegrated in 74 seconds as shown in Examples. A tablet is completely or partially soaked in water in a small-type laboratory dish. Since motion of tongue adds to disintegration in oral cavity, a disintegrating time was measured by adding weak shaking to this small-type laboratory dish.

Shaking machine SA-31-type (manufactured by Yamato Scientific)

Vibration distance, 4 cm

Shaking times: 40/min. = 1/1.5 seconds (minimum setting value)

[0016] Using a sold plain tablet A (weight 200 mg, diameter 8 mm) and B (weight 280 mg, diameter 9 mm) having the almost same size as that of the rapidly disintegrating tablet (weight 200 mg, diameter 8 mm) of the present invention, a test was performed under the aforementioned condition, and the results thereof are shown in Table 1. It is clear that these sold plain tablets can not said to be a rapidly disintegrating tablet. The rapidly disintegrating tablet of the present invention is remarkably different from sold plain tablets.

Table 1

	Weight (mg)	Diameter (mm)	Hardness (km)	Disintegrating test (Japanese Pharmacopoeia)	Disintegrating time Laboratory dish method
Sold tablet A	200	8	4.0	Satisfactory (10 min.)	Retained original shape even after 1 hour.
Sold tablet B	280	9	16.5		Partially disintegrated by 1 hour

[0017]

[Examples] The present invention will be specifically explained by way of Examples below.

[0018]

[Example 1] Ratio of slightly substituted hydroxypropylcellulose and crystalline cellulose to be incorporated of 3:7 (when slightly substituted hydroxypropylcellulose 1, 1:2.3 in obtained).

Ingredient

Crystalline cellulose	69.3%
Slightly substituted hydroxypropylcellulose	29.7%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 2.

Table 2 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	5.5	7.8	10.1	14.1	15.3
Disintegrating time (sec)	25.3	31.4	33.1	47.7	56.1

[0019]

[Example 2] Ratio of slightly substituted hydroxypropylcellulose and crystalline cellulose of 1:3.5

Ingredient	Amount
Crystalline cellulose	77.0%
Slightly substituted hydroxypropylcellulose	22.0%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 3.

Table 3 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	4.7	7.1	8.9	11.7	14.5
Disintegrating time (sec)	31.7	36.8	40.3	58.2	73.7

[0020]

[Example 3] Ratio of slightly substituted hydroxypropylcellulose and crystalline cellulose of 1:4

Ingredient	Amount
Crystalline cellulose	79.2%
Slightly substituted hydroxypropylcellulose	19.8%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 4.

Table 4 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	5.7	8.3	11.7	14.1	17.0
Disintegrating time (sec)	27	28.6	29.2	32.7	40.7

[0021]

[Example 4] Ratio of slightly substituted hydroxypropylcellulose and crystalline cellulose of 1:8

Ingredient	Amount
Crystalline cellulose	88.0%
Slightly substituted hydroxypropylcellulose	11.0%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better

relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 5.

Table 5 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	5.9	9.7	11.6	13.7	15.6
Disintegrating time (sec)	23.3	37.7	38.6	41.7	56.9

[0022]

[Example 5] Ratio of slightly substituted hydroxypropylcellulose and crystalline cellulose of 1:9

Ingredient	Amount
Crystalline cellulose	89.1%
Slightly substituted hydroxypropylcellulose	9.9%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 6.

Table 6 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	5.2	8.8	11.3	14.6	18.0
Disintegrating time (sec)	22.3	35.6	42.8	27.2	36.2

[0023]

[Example 6]

Formulation in which meclizine hydrochloride is added 10% of meclizine hydrochloride as well as a ratio of slightly

substituted hydroxypropylcellulose and crystalline cellulose of 3:7 (when slightly hydroxypropylcellulose is 1, 1:2.3 is obtained).

Ingredient	Amount
Meclizine hydrochloride	10.0%
Crystalline cellulose	63.3%
Slightly substituted hydroxypropylcellulose	26.7%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 7.

Table 7 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	3.4	4.6	6.2	7.8	11.8
Disintegrating time (sec)	36.5	27.36	32.5	40.1	54.0

[0024]

[Example 7]

Formulation in which meclizine hydrochloride is added 10% of meclizine hydrochloride as well as a ratio of slightly substituted hydroxypropylcellulose and crystalline cellulose of 1:4 .

Ingredient	Amount
Meclizine hydrochloride	10.0%
Crystalline cellulose	71.2%

Slightly substituted hydroxypropylcellulose	17.8%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 8

Table 8 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	4.5	6.2	8.9	11.7	13.2
Disintegrating time (sec)	20.5	22.0	26.8	28.9	31.5

[0025]

[Example 8]

Formulation in which meclizine hydrochloride is added 10% of meclizine hydrochloride as well as a ratio of slightly substituted hydroxypropylcellulose and crystalline cellulose of 1:9.

Ingredient	Amount
Meclizine hydrochloride	10.0%
Crystalline cellulose	80.1%
Slightly substituted hydroxypropylcellulose	8.9%
Magnesium stearate	1.0%

The aforementioned powders were uniformly mixed, which was compressed with a compression machine. The better relationship between disintegrating time, compression pressure and hardness was obtained as shown in Table 9

Table 9 Average of n=3

Compression pressure (kgf)	100	150	200	250	300
Hardness (kg)	4.5	6.2	8.9	11.7	13.2
Disintegrating time (sec)	20.5	22.0	26.8	28.9	31.5

[0026]

[Effects of the invention] The rapidly disintegrating tablet of the present invention can provide a tablet which has a disintegrating time of 70 seconds or shorter in a disintegrating test using a small-type laboratory dish and is rapidly disintegrated in around a few tens second by saliva (small amount of water) in oral cavity. As a result, administration of a tablet to senior having the weak swallowing ability and administration of a tablet without no water become possible.